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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,528	WILHELM ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment submitted on May 3, 2006. Claims 1-19 are pending in the application and are being examined on the merits herein.

The rejection of claims 1-9 and 16-19 under 35 U.S.C. 112, first paragraph, is being withdrawn in view of Applicant's amendments to the claims to recite that the malignant tumors, metastases and/or lung foci are "urokinase associated."

The terminal disclaimers filed on May 3, 2006 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent Nos. 6,624,169 and 6,680,320 have been reviewed and is accepted. The terminal disclaimer has been recorded. Accordingly, the obviousness-type double patenting rejections made over these references are being withdrawn.

Applicant's arguments regarding the rejection of the claims under 35 U.S.C. 103(a) have been fully considered but they are not persuasive. The claims remain rejected as set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 8-12, 15 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article entitled "Prevention of Breast Cancer Growth, Invasion and Metastasis by Antiestrogen Tamoxifen Alone or in Combination with Urokinase Inhibitor B-428" by Xing et al, Cancer Research 57, 3585-3593, 1997 (of record) in view of the PENTAPHARM Product Catalog 1998 (of record) or the PENTAPHARM Product Catalog 1997 (as provided by Applicants in the IDS dated December 6, 2005.)

Xing et al. teaches a method of preventing breast cancer growth, invasion and metastasis to lungs and lymph nodes (see page 3585, introduction, and page 3589, first full paragraph, in particular), using a urokinase inhibitor in a pharmaceutically acceptable carrier continuously over the course of two weeks (see page 3586, third paragraph, in particular) and in combination with a cytotoxic substance (tamoxifen) (see page 3585, materials and methods, in particular.) Xing et al. teaches that the uPA/uPAR system plays a key role in tumor invasion and metastasis, and inhibition of cell surface uPA activity is an attractive therapeutic target for controlling cellular

invasiveness in cancer (see page 3585, right hand column, second full paragraph, in particular.)

Thus, Xing et al. teaches providing urokinase inhibitors for the treatment of malignant tumors and metastases, as in claims 1, 18 and 19, including tumors that affect the lymph nodes, as in claim 3, and thus the lymphatic system, as in claim 2, and teaches administering a cytotoxic substance as in claim 5. Xing et al. also teaches treating malignant tumors that are breast tumors, as in claim 8. Regarding claim 9, Xing et al. teaches continuous administration of the urokinase drug, and teaches that the TAM can be administered daily (see page 3586, third full paragraph, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the dosage regimen for the composition, according to the guidance provided by Xing et al, to provide the desired treatment. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 10-12, Xing et al. teaches a urokinase inhibitor with a pharmaceutically acceptable carrier and tamoxifen (cytotoxic substance.) Regarding claim 15, Xing et al. teaches a minipump comprising a urokinase inhibitor and separate administration of tamoxifen (see page 3585, third full paragraph, in particular), and thus

teaches a "kit" having separate containers for the urokinase inhibitor and cytotoxic substance.

Xing et al. does not specifically teach providing a urokinase inhibitor that is Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide, the L enantiomer thereof, or a pharmaceutically acceptable salt thereof.

The 1998 PENTAPHARM Product Catalog teaches the hydrochloride salt of Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide. The catalog also describes the compound in the following manner: "Pefabloc® uPA is a low molecular weight synthetic inhibitor for urokinase." It is well known in the pharmaceutical arts that a compound must be in the form of a weak acid in order for it to go into a pharmaceutical carrier solution; therefore, it is evident that PENTAPHARM (a company operating under a descriptive and suggestive name giving the impression of being a pharmaceutical manufacturer) manufactured the hydrochloride salt form prospectively in consideration for its use as a pharmaceutical. The 1997 PENTAPHARM Product Catalog as submitted by Applicants provides the same information for Pefabloc® uPA on page 23 of the catalog.

Therefore, it would have been obvious to one of ordinary skill in the art to provide the urokinase inhibitor compound of PENTAPHARM in the composition and/or method

of treatment of Xing et al, because Xing et al. teaches that a treatment method with urokinase inhibitors decreases tumor volume and metastasis, and PENTAPHARM teaches a compound that acts as a urokinase inhibitor. Thus, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the urokinase inhibitor of PENTAPAHRM in the cancer/tumor and metastasis treatment method and/or composition of Xing et al, with the expectation of providing a suitable treatment for the malignant tumors and metastasis. Accordingly, claims 1-3, 5, 8-12, 15 and 18-19 are obvious over the teachings of the references.

Claim 4 is rejected under 35 U.S.C. as being unpatentable over Xing et al, in view of the PENTAPHARM Product Catalog 1998 or 1997, as applied to claims 1-3, 5, 8-12, 15 and 18-19 above, and further in view of the reference "Cancer Principles and Practice of Oncology," fifth Edition, by DeVita et al. Lippincott Williams and Wilkins 1997 (of record.)

Xing et al. and the PENTAPHARM catalogs are applied as discussed above for claims 1-3, 5, 8-12, 15 and 18-19 above, and teach a treatment for breast cancer and tumors of the lungs and lymph nodes with the composition as claimed. Xing et al. and the PENTAPHARM catalogs do not specifically teach that the lymphnodes are selected form the group consisting of axillary and intraperitoneal lymph nodes.

DeVita et al. teaches that it is well known in the art that carcinomas frequently spread and grow in the lymphatic system (see page 139, first full paragraph) and that the ultimate event that leads to mortality in breast cancer is metastasis (see page 1549 first sentence under Angiogensis and Metastasis, in particular.) DeVita et al. teaches that the axillary lymph nodes are affected by the metastasis (see page 139, paragraph bridging left and right hand columns, in particular.) It is furthermore noted that DeVita et al. teach that investigations have focused on plasminogen of secreted plasminogen activator urokinase (see page 150, second full paragraph, in particular) and that metastasis of tumors depends on a balance between enzymes and their inhibitors (see page 1550, third full paragraph, in particular.)

Accordingly, it would have been obvious to provide the composition of Xing et al. and the PENTAPHARM catalogs for the treatment of axillary lymph nodes, as in DeVita et al, because Xing et al. and the PENTAPHARM catalogs teach the composition for the treatment of tumors and metastasis involving lymph nodes, such as metastasized breast cancer, in which urokinase is implicated, and DeVita et al. teaches that the axillary lymph nodes are affected in the metastasis of breast cancer, and that uPA is implicated in the metastasis of the cancers. Thus, one of ordinary skill in the art would have found it obvious to treat axillary lymph nodes with the composition with the expectation of providing a suitable treatment for metastasized tumors affecting the axillary lymph nodes. Accordingly, claim 4 is obvious over the references.

Claims 6-7 and 13-14 are rejected under 35 U.S.C. as being unpatentable over Xing et al, in view of the PENTAPHARM Product Catalog 1998 or 1997, as applied to claims 1-3, 5, 8-12, 15 and 18-19 above, and further in view of U.S. Patent No. 5,736,129 to Medenica et al. (of record.)

Xing et al. and the PENTAPHARM catalogs are applied as discussed above for claims 1-3, 5, 8-12, 15 and 18-19 above, and teach a treatment for breast cancer and tumors of the lungs and lymph nodes with the composition as claimed, and including tamoxifen (cytotoxic agent.) Xing et al. and the PENTAPHARM catalogs do not specifically teach providing a cytotoxic agent that is one of the specific agents recited in claims 6-7 and 13-14.

Medenica et al. teaches a method of treating cancer by the use of a multi-chemotherapeutic drug regime (see abstract, in particular) that makes use of cisplatin (see column 16, lines 8-15, in particular), carboplatin (see column 9, lines 65-67, in particular), doxorubicin (see column 8, lines 39-45, in particular), epirubicin (see column 22, line 28, in particular), 5-fluorouracil (see column 17, lines 11-16, in particular) and paclitaxel (see column 10, lines 24-29, in particular.) Medenica et al. teaches that the regimen is suitable for treating various types of tumors and their metastases (see abstract, in particular), including breast cancer and other types of metastasized cancers (see Experiments 8 and 9, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to combine the agents of Medenica et al. with the treatment method of Xing et al. and the PENTAPHARM catalogs, because both are directed to the treatment of tumors and their metastases, such as breast cancer tumors and metastases. Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.)

Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xing et al, in view of the PENTAPHARM Product Catalog 1998 or 1997, as applied to claims 1-3, 5, 8-12, 15 and 18-19 above, and further in view of U.S. Patent No. 5,449,663 to Haim I. Bicher, issued September 12, 1995.

Xing et al. and the PENTAPHARM catalogs are applied as discussed above for claims 1-3, 5, 8-12, 15 and 18-19 above, and teach a treatment for breast cancer and tumors of the lungs and lymph nodes with the composition as claimed, and including tamoxifen (cytotoxic agent.) Xing et al. also teaches providing tamoxifen, which is a cytotoxic agent, as recited in claim 17. Xing et al. and the PENTAPHARM catalogs do not specifically teach surgically removing the primary tumor from the patient.

Bicher teaches that surgery is one of the major approaches to the treatment of cancer (see column 2, lines 10-30, in particular), and can be combined with chemotherapeutic treatment (see column 2, line 65 through column 3, line 20, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to surgically remove the tumor, according to the teachings of Bicher, in combination with providing the chemotherapeutic composition of Xing et al. and the PENTAPAHRM catalogs, because the Xing et al. and PENTAPHARM teach the treatment of tumors and metastases, and Bicher teaches that surgery is a primary means of treating tumors. Thus, one of ordinary skill would have found it obvious to perform surgery in combination with the method of the Xing et al. and PENTAPHARM, with the expectation of providing a suitable treatment for malignant tumors.

Response to Arguments

Applicant's arguments filed May 3, 2006 have been fully considered but they are not persuasive.

In particular, Applicant's argue that the cited art does not teach what urokinase inhibitors would be suitable for treatment *in vivo*. Applicant's argue that the Xing et al. reference discloses a particular urokinase inhibitor for treatment but does not suggest that any or all urokinase inhibitors are useful as antitumor agents, and thus one of

ordinary skill in the art would not have found it obvious to provide the specific urokinase inhibitor as taught in the Pentapharm product catalogs. The Examiner respectfully disagrees. Xing et al. teaches that "increased uPa production by tumor cells and their surrounding stroma is associated with higher invasive and metastatic potential in human malignancies" (see page 3585, right hand column, first full paragraph, in particular) and that "because the uPA/uPAR system plays a key role in tumor invasion and metastatis, inhibition of cell surface uPA activity is an attractive therapeutic target for controlling cellular invasiveness in cancer" (see page 3585, right hand column, second full paragraph, in particular.) Thus, Xing et al. is directed to the treatment and/or inhibition of tumors and metastasis with urokinase inhibitors in general, and to that end discloses the successful results of an exemplary urokinase inhibitor in an *in vivo* cancer model. Accordingly, based on the general teachings of Xing et al. as to the efficacy of urokinase inhibitors in cancer treatment, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the specific urokinase inhibitor of the Pentapharm catalogs in the treatment of Xing et al, with the expectation of providing a suitable tumor/metastasis growth inhibiting treatment.

Applicants further argue that the Pentapharm catalog does not teach that the specific compound taught therein would have *in vivo* urokinase activity, and argue that it would not be obvious to one of ordinary skill in the art to provide a compound having proven results only for *in vitro* activity as an *in vivo* active agent, due to the

unpredictability in the pharmaceutical arts. The Examiner respectfully disagrees. In particular, the Examiner notes that Xing et al. provides motivation for one of ordinary skill in the art to provide urokinase inhibitors for the treatment and/or inhibition of tumors and metastasis with a reasonable expectation of success. Applicants further argue that before a compound having in vitro activity can be used in vivo, the compound "must be shown to have no cytotoxicity, and must be taken up by the organism and must have efficacy" (paragraph bridging pages 7-8 of Amendment submitted May 3, 2006.) However, the Examiner maintains that methods of determining cytotoxicity are routine to those of ordinary skill in the art, and in the instance of a single compound as presently claimed, would not require undue experimentation on the part of one of ordinary skill in the art. Methods of showing the *in vivo* efficacy of the urokinase inhibitor compound are also known and are not deemed to require undue experimentation. For example, the Xing et al. reference itself teaches both a cancer model and method of testing urokinase inhibitors for the treatment and/or inhibition of tumors and metastasis, and thus it is considered that the testing of the urokinase inhibitor for the desired *in vivo* treatment efficacy would require only routine experimentation on the part of one of ordinary skill in the art.

The Examiner has fully considered the declaration filed under 37 CFR 1.132 and signed by Mr. Olivier Kapp, manager of the legal department at Pentapharm, on April 16, 2006, stating that the Pefabloc® series was "sold in 1997 and 1998 for use only in research, analytical applications and purification processes," and was "not advertised,

sold as or intended to be sold as a pharmaceutical active ingredient" (see paragraphs 1 and 2 of declaration.) The Examiner acknowledges that Pentapharm did not advertise or sell the compound that is disclosed in the 1997 and 1998 catalogs as having urokinase inhibition activity, as a pharmaceutical agent. However, the Examiner maintains that, in view of the urokinase inhibitor treatment teachings of Xing et al, it would nonetheless be obvious to provide the compound having the urokinase inhibiting activity in the treatment and/or inhibition of the growth of tumors and metastasis.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. In particular, the articles entitled "The Urokinase-Type Plasminogen Activator System in Cancer Metastasis: A Review" by Andreasen et al, 1997, Int. J. Cancer, 72, pages 1-22, and "Urokinase receptor antagonists: Novel Agents for the Treatment of Cancer" by Weidle et al, 1998, Expert Opinion on Investigational Drugs, 7(3), pages 391-403, describe the involvement of the urokinase-type plasminogen activator system in cancer, tumor growth and metastatis, and therapeutic potential for drugs that interfere with the action of the system in cancers.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

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SUPERVISORY PATENT EXAMINER